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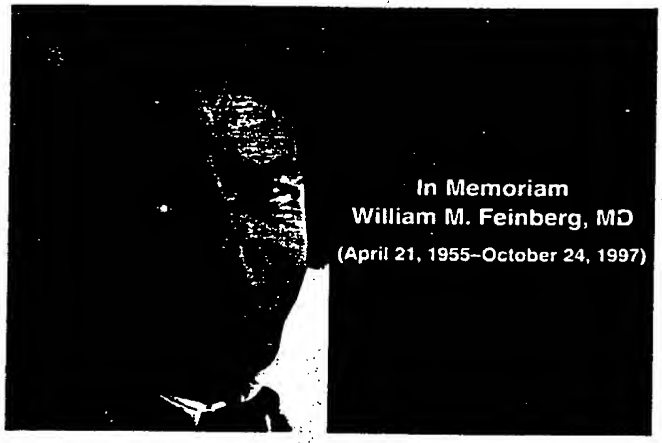

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U.S. Serial No.: 09/374,586
Filed: August 13, 1999
Group Art Unit: 1633

Exhibit 6

Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke

Feasibility, Safety, and Efficacy in the First Year of Clinical Practice

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Background and Purpose—The feasibility, safety, and efficacy of intravenous tissue plasminogen activator (t-PA) for patients with acute ischemic stroke in clinical practice need to be assessed.

Methods—We initiated a prospective open-label study at a university hospital and two community hospitals in Houston, Tex, immediately after the publication of the National Institute of Neurological Disorders and Stroke (NINDS) t-PA study. A total of 30 patients, age 32 to 90 years, were treated with 0.9 mg/kg of intravenous t-PA (maximum dose, 90 mg) within 3 hours of acute ischemic stroke between December 1995 and December 1996.

Results—Six percent (6%) of all patients hospitalized with ischemic stroke received intravenous t-PA at the university hospital and 1.1% at the community hospitals. The rates of total, symptomatic, and fatal intracerebral hemorrhage were 10%, 7%, and 3%. Thirty-seven percent (37%) of patients recovered to fully independent function. The average time from stroke onset to emergency department arrival was 57 minutes; emergency department arrival to computed tomography scan 41 minutes; and computed tomography scan to administration of treatment 59 minutes.

Conclusions—When treatment guidelines are carefully followed in an urban hospital setting, intravenous t-PA for acute ischemic stroke is feasible and shows safety and efficacy comparable to the results of the NINDS study. (***Stroke.*** **1998;29:18-22.)**

Key Words: cerebral hemorrhage ■ cerebral infarction ■ emergency medical services ■ thrombolytic therapy

Tissue plasminogen activator (t-PA) was demonstrated to be effective in the first 3 hours after acute ischemic stroke in a pivotal randomized clinical trial sponsored by the National Institutes of Neurological Disorders and Stroke (NINDS).[1] Questions regarding the safety and efficacy of t-PA in clinical practice still persist, in part because a number of other multicenter trials, using alternative thrombolytic protocols and time windows >3 hours, failed to replicate the results of the NINDS study,[2-5] mainly because of high rates of intracerebral hemorrhage (ICH) and/or ICH-related mortality. The incidence of ICH may be influenced by the time to treatment, the presence of CT hypodensity,[6] the thrombolytic agent and dose, and the combination of thrombolysis with heparin or aspirin.

We initiated a postmarketing survey of t-PA for stroke immediately after the publication of the NINDS study at a university hospital and two community hospitals in Houston, Tex. The feasibility of evaluating and treating patients in the emergency department within 3 hours of stroke onset is examined. We assess the outcome of patients treated with intravenous t-PA, including the incidence of intracerebral hemorrhage and other adverse events. Predictors of outcome are analyzed. The overall purpose of our phase IV study of t-PA is to report the current clinical practice of thrombolytic therapy for acute stroke.

Subjects and Methods

We prospectively studied all patients (n=30) who were treated with intravenous t-PA for stroke at a university hospital and two community hospitals in Houston between December 1995 and December 1996. The three hospitals were linked by a communication system to a single stroke treatment team made up of four neurology faculty members, three fellows, and a nurse coordinator. In 28 of 30 cases, a member of the stroke team examined the patient before the decision to administer thrombolysis. The stroke team provided consultation by telephone for the other two patients. The treating physician was a stroke fellow in 23 cases, a stroke faculty member in 5 cases, an emergency physician in 1 case, and a neurology resident in 1 case.

We used paramedic, emergency department, and hospital records to assess time of symptom onset, time of arrival in the emergency department, time of CT examination, and time of t-PA administration. Demographic characteristics, stroke risk factors, baseline CT scans, and blood pressure measurements were recorded, and the baseline NIH Stroke Scale was extrapolated from the recorded neurological examination.

Each patient received 0.9 mg/kg of intravenous t-PA up to a maximum of 90 mg, based on estimated or actual weight. Ten percent of the dose was given as a bolus, and the remainder infused over 1 hour. Heparin and aspirin were withheld for the first 24 hours after t-PA administration in all patients. As a rule, systolic blood pressures

Received August 7, 1997; final revision received October 7, 1997; accepted October 28, 1997.
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>185 mm Hg and diastolic blood pressures >110 mm Hg were treated with intravenous antihypertensive medications such as labetalol, nicardipine, or enalapril.

Results of follow-up CT or MRI scans were recorded as well as use of aspirin, ticlopidine, heparin, warfarin, or antihypertensive drugs during hospitalization. Serious hemorrhages or transfusions were noted, and the maximal blood pressure during t-PA infusion and the first 24 hours was recorded. Stroke subtype, determined after diagnostic evaluation, was classified as cardioembolic, large vessel, small vessel, other determined pathogenesis, or cryptogenic, using the TOAST criteria.[7] We obtained telephone or clinic follow-up with the patient (and caregiver, if necessary) on all 30 cases in December 1996 and assessed the Barthel Activities of Daily Living Index and Modified Rankin Disability Scale. Use of the telephone interview for assessing stroke outcome has been previously validated.[8,9] Inquiry was made into the number of weeks spent in acute inpatient rehabilitation, outpatient rehabilitation, skilled nursing facilities, nursing homes, and professional home care.

Logistic regression was performed to determine predictors of outcome. For the purposes of the analysis, a good outcome was defined as a Barthel Activities of Daily Living Index of ≥75. Potential predictors were tested first in univariate regression. A stepwise model-building procedure was then carried out,[10] and covariates significant at the .10 level were included in the final multivariate regression model. Significance was calculated by the likelihood ratio test. Potential predictors of intracerebral hemorrhage were analyzed by Fisher's exact test (for dichotomous variables) or univariate logistic regression. Multivariate regression for ICH was not performed because of the small number of such patients.

Results

Thirty patients received intravenous t-PA for stroke between December 1995 and December 1996. The stroke team was notified of 267 patients suspected of having an acute stroke during this period.[11] The most common reasons for disqualification from thrombolytic therapy were the time limit (37%), intracerebral hemorrhage (22%), minor or rapidly resolving symptoms (19%), and a nonstroke diagnosis (12%). Several patients met multiple criteria for exclusion, but only one was tabulated per patient. In many cases, patients could be excluded by telephone. Twenty-three patients were treated with t-PA at the university hospital out of 405 discharged with an ICD-9 diagnosis of ischemic stroke during the same period (6%). The rates of t-PA use at the two community hospitals were 5 of 302 and 2 of 328 (1.7% and 0.6%, respectively). Risks and benefits were discussed with the family of all candidates before t-PA was given. There were no refusals of treatment for patients who were otherwise eligible.

Fifty-three percent (53%) of the patients treated were male. The mean age was 66±15 years, ranging from 32 to 90. Fifty-three percent (53%) were white, 33% black, 7% Hispanic, and 3% Asian. Thirty percent (30%) were taking aspirin at the time of the stroke. Other baseline characteristics are listed in Table 1.

More than half of patients had the onset of symptoms between noon and 6 PM (Table 2). The average time from onset of symptoms to arrival in the emergency department was 57 minutes. Mean duration from arrival in the emergency department to CT scanning was 41 minutes (39 minutes at the university hospital, 47 minutes at the affiliate hospitals). The average "door-to-needle" time was 100 minutes (94 minutes at the university hospital, 118 minutes at the affiliate hospitals). The average total time from stroke onset to administration of t-PA was 157 minutes (range, 97 to 220). Although the intention was to treat within 3 hours in each case, t-PA was actually administered beyond the 180-minute mark in 3 patients (10%) at 192, 200, and 220 minutes. Two of the time violations occurred in a community hospital.

The treating physician or radiologist recognized early ischemic changes in four baseline CT scans (13%). In two cases, a

TABLE 1. Demographic and Pretreatment Characteristics (n=30)

Age (mean±SD)	66±15 y; range, 32 to 90
Sex	16 (53%) male/14 (47%) female
Race	16 (53%) White
	11 (37%) Black
	2 (7%) Hispanic
	1 (3%) Asian
Hypertension	16 (53%)
Aspirin	9 (30%)
Atrial fibrillation	9 (30%)
Current smoker	8 (28%)
Myocardial infarction	7 (24%)
Congestive heart failure	6 (20%)
Prior stroke	4 (13%)
Diabetes mellitus	3 (10%)
Hypercholesterolemia	2 (7%)
Early CT ischemic change	4 (13%)
Mean admission blood pressure	156/88 mm Hg
Mean maximum pretreatment blood pressure	166/90 mm Hg
NIH Stroke Scale (mean±SD)	14±8; range, 3 to 36
Stroke subtype	
Cardioembolic	9 (30%)
Large vessel	8 (27%)
Small vessel	2 (7%)
Cryptogenic	5 (17%)
Other	3 (10%)
Undetermined	3 (10%)

NIH indicates National Institutes of Health.

TABLE 2. Time Parameters (n=30)

Stroke Onset	
Midnight to 6 AM	1 (3%)
6 AM to noon	6 (20%)
Noon to 6 PM	16 (53%)
6 PM to midnight	7 (23%)

	University Hospital n=22* (mean±SD)	Community Hospitals n=7 (mean±SD)	Overall n=29* (mean±SD)
Time to emergency department	57±28 min	58±31 min	57±28 min
Emergency room to CT time	39±23 min	47±13 min	41±21 min
Emergency room to tissue plasminogen activator time	94±30 min	118±34 min	100±32 min

*One patient in the hospital at the time of stroke onset is excluded.

TABLE 3. Outcome (n=30)

Mean maximum blood pressure during treatment	159/88 mm Hg
Mean maximum blood pressure during 24 h after treatment	168/92 mm Hg
Received antihypertensive therapy	17 (57%)
Received heparin or warfarin	16 (53%)
Received antiplatelet therapy	12 (40%)
Received transfusion	3 (10%)
Length of hospitalization (mean±SD)	9±9 d
Infarct on follow-up computed tomography or magnetic resonance imaging	19 (63%)
Hemorrhagic conversion (total)	3 (10%)
Symptomatic intracerebral hemorrhage	2 (7%)
Fatal intracerebral hemorrhage	1 (3%)
Mean length of follow-up (mean±SD)	5±4 mo

	Number of Patients	Average Stay per Patient
Inpatient rehabilitation	13 (43%)	3.4wk
Outpatient rehabilitation	12 (40%)	14.4wk
Skilled nursing facility	1 (3%)	2 wk
Nursing home	1 (3%)	44 wk
Professional home care	4 (13%)	18.8wk

hypodensity limited to less than one third of the middle cerebral artery territory was present, indicating a subacute infarct. In the other two cases, the CT changes were subtle: loss of gray-white differentiation, insular ribbon sign, indistinctness of the basal ganglia, and/or mild sulcal effacement. No patient showed acute hypodensity that involved greater than a third of the middle cerebral artery territory, that is, two or more of the following regions: the basal ganglia, frontal, parietal, and temporal lobes.

The mean baseline NIH Stroke Scale was 14 (range, 3 to 36). Stroke subtype by final diagnosis was cardioembolic in 30%, large vessel in 27%, small vessel in 7%, cryptogenic in 17%, undetermined in 10%, and other in 10%. The other etiologies—established after hospital admission—included bacterial endocarditis in one patient, concomitant large vessel and cardiac disease in one patient, and suspected psychogenic hemiparesis in the third. Seventeen percent (17%) were vertebrobasilar strokes.

Follow-up CT or MRI was performed in all patients except one who had complete resolution of symptoms by 24 hours. Sixty-three percent (63%) showed an ischemic infarct (Table 3). Three developed ICH: one fatal intrainfarct hematoma (3%), one nonfatal symptomatic hemorrhage (3%) in a location remote from the initial infarct, and one mild hemorrhagic infarct conversion unaccompanied by neurological worsening (3%). The symptomatic hemorrhages developed 3 and 13 hours after thrombolytic treatment and were managed conservatively.

The mean duration of follow-up in our study was 5 months (SD, 4). Thirty-seven percent of patients recovered to fully independent function in activities of daily living (Barthel Index, 100; Table 4). Thirty percent of patients had no disability at follow-up (Modified Rankin Scale 0–1). Another

TABLE 4. Functional (Barthel Index) and Disability (Modified Rankin Scale) Outcomes (n=30)

Barthel Index	95-100	55-90	0-50	Died
Houston	37%	23%	17%	23%
NINDS	50%	16%	17%	17%

Modified Rankin	0-1	2-3	4-5	Died
Houston	30%	33%	13%	23%
NINDS	39%	21%	23%	17%

NINDS indicates National Institute of Neurological Disorders and Stroke.

33% had mild or moderate disability but were ambulatory (Modified Rankin Scale 2-3). Thirteen percent (13%) were moderately to severely disabled and unable to walk (Modified Rankin Scale 4–5), and 23% were dead. Of the deaths, two were caused by bleeding complications: an intracerebral hemorrhage and a hemorrhagic pericardial tamponade. The patient with fatal hemopericardium had no previous cardiac history. The other causes of death were neurological in three patients (two with basilar artery infarcts and one with a malignant middle cerebral artery stroke) and nonneurological in two (pneumonia and ischemic heart disease). There was one serious nonfatal hemorrhagic event, also a hemopericardium, occurring in a patient who received thrombolysis 16 days after coronary artery bypass surgery. A total of three patients (10%) received blood transfusions. The effects of various risk factors on the likelihood of a favorable outcome in a multivariate model are shown in Table 5.

All three intracerebral hemorrhages occurred in women with cardioembolic stroke who had early ischemic changes on initial CT. ICH occurred in 1 of 23 patients treated by fellows, 2 of 5 patients treated by faculty, and none of 2 patients treated by emergency physicians or neurology residents. The inci-

TABLE 5. Adjusted Effects on Odds of Favorable Outcome (Barthel Index ≥75) by Multivariate Logistic Regression (n=30)

	Odds Ratio	P	95% Confidence Interval
NIH score (5 points)	.313	.003	.010-.983
Mean arterial pressure (10 mm Hg)*	.445	.02	.194-1.02
Age (10 y)	.467	.10	.172-1.27
Cardioembolic cause	.139	.10	.011-1.74
Variables with no significant effect on outcome			
Aspirin			
Early CT abnormality			
Follow-up duration			
Race			
Sex			
Time to treatment			

NIH indicates National Institutes of Health.
*Maximum pretreatment mean arterial pressure.

dence of hemorrhage was 2 of 23 in patients treated at the university hospital and 1 of 7 in patients treated at a community hospital. None of the 3 patients treated beyond the 180-minute mark developed ICH. The two factors significantly associated with ICH by Fisher's exact test were early CT ischemic changes (P=.002) and cardioembolic stroke (P=.04).

Discussion

There were notable similarities between the results of this study and those of the NINDS t-PA trial. The mean NIH Stroke Scale in our study was 14, identical to the average stroke severity score in the NINDS study. The mean age was 66 years, compared with 67 in the NINDS study. The rates of total, symptomatic, and fatal intracerebral hemorrhage in our study were 10%, 7%, and 3%, respectively, compared with 10%, 6%, and 3% in the treated group in the NINDS trial. The safety of t-PA demonstrated in the multicenter NINDS clinical trial can be replicated in clinical practice when the guidelines are observed.

An obvious difference between our study and the NINDS trial is that half of the patients randomized in the NINDS study were treated within 90 minutes of stroke onset as mandated by the protocol, whereas the earliest treatment in our study was 97 minutes. Of note, the response to t-PA in the NINDS trial was the same for patients who received treatment under 90 minutes and those who received treatment between 90 and 180 minutes. Over half of our patients had the onset of symptoms in the afternoon despite the fact that consultation with the stroke treatment team was readily available 24 hours a day, a major reason being the exclusion of patients who developed symptoms during sleep.

Patients arrived in the emergency department an average of 57 minutes after onset of symptoms. The CT scan was performed an average of 41 minutes after arrival in the emergency department. Another 59 minutes elapsed on average between the CT and initiation of thrombolysis. The most common reasons for delay of treatment were queues in the CT scanner, travel by the stroke team member to the hospital, marked acute hypertension requiring treatment, drug preparation, agitation of patients requiring sedation for CT scan, delays in laboratory results, difficulty in obtaining venous access, consultations with other physicians, and locating family members. Recent NIH consensus guidelines recommend a door-to-needle time of 60 minutes or less for acute stroke patients.[12]

The NINDS trial excluded patients with acute myocardial infarction, significant neurological deficits residual from previous strokes, or any illness that would interfere with assessment of patient outcome, whereas FDA guidelines did not bar us from treating such patients. We administered thrombolysis to 4 individuals (13%) who had baseline disability (Modified Rankin Scale $\geq$2) resulting from prior strokes or impaired cardiac function. The overall outcome scores on the Barthel Activities of Daily Living Index and Modified Rankin Disability Scale are compared with those of the t-PA patients in the NINDS trial in Table 4.

The 3-month mortality in our study was 20% (one subject died after 3 months), compared with 17% in the NINDS trial. The number of patients left severely impaired was similar (17% with Barthel Index 0–50 in both studies). The proportion of patients who made a complete or near-complete recovery in our study was somewhat less than that of the NINDS t-PA patients, but this is not surprising given our inclusion of patients with previous disability. Excluding these subjects, 35% of our patients achieved a Modified Rankin Scale of 0 or 1, compared with 39% of the NINDS t-PA group. Only one patient (3%) was admitted to a skilled nursing facility and one patient (3%) to a nursing home, consistent with the finding in the NINDS study that patients receiving t-PA required less chronic care.[13]

The variables that had the most significant effect on outcome in multivariate logistic regression were the NIH Stroke Scale, the mean arterial pressure, age, and a cardioembolic stroke subtype. Adjusting for the other variables in the model, a five-point increase in the NIH Stroke Scale decreases the odds of a favorable outcome by 69%. A cardiac cause of stroke increases the odds of a poor outcome, as do a high pretreatment mean arterial pressure and advanced age. Patients with cardioembolic strokes had poorer outcomes independent of stroke severity and age largely because of cardiac comorbidity (eg, congestive heart failure). We found that these patients as a group had lengthier hospital stays, often because of cardiac complications. The effect sizes have wide confidence intervals because of the relatively small sample size, but our findings are consistent with known predictors of stroke outcome in general and do not indicate which patients should not receive t-PA. An elderly patient or one with a severe stroke may have a poorer overall prognosis, but it is irrational to withhold therapy if the margin of benefit is the same. Post hoc analysis of the NINDS data showed t-PA to be beneficial for patients in all strata of age, stroke severity, and stroke subtype.[14]

Attempting to predict hemorrhagic conversion in our study is hazardous because of the small numbers of ICH (n=3), but early CT ischemic changes and a cardioembolic causes proved to be significant risk factors in univariate analysis. The fatal ICH occurred in a patient who, in retrospect, had relatively advanced ischemic changes on baseline CT. Stroke severity, pulse pressure, and early CT changes were predictors of ICH in post hoc analysis of the NINDS data.[15] The occurrence of hemopericardium in two of our patients indicates that caution should be exercised when treating patients with acute myocardial infarction or recent coronary artery bypass graft surgery. Hemopericardium should be suspected in patients who develop unexplained hypotension after receiving t-PA.

Our data reflect the outcome of patients managed in urban hospitals by a stroke team experienced in treating acute stroke patients with t-PA. While there is no particular reason to believe that the same results could not be duplicated in other practice settings, the generalizability of our findings in other environments remains to be established. There can be no doubt, however, that the ability to perform rapid and accurate neurological assessment, CT examination, and cardiovascular monitoring are essential to the success of thrombolytic therapy for stroke.

Our experience in Houston with intravenous t-PA for acute ischemic stroke in the first year of FDA approval demonstrates that the therapy is feasible and safe in an urban hospital setting. Patients can be successfully triaged, selected, and treated

outside the scope of a randomized clinical trial, although the present door-to-needle time of 100 minutes leaves room for improvement. Approximately 6% of stroke patients currently receive t-PA at our university hospital, a considerably higher percentage than that in the community.

Acknowledgments

We gratefully acknowledge the physicians, nurses, and staff of Hermann Hospital, Memorial Southwest Hospital, and Memorial Northwest Hospital in Houston, Tex, and the Houston Fire Department and Emergency Medical Services.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
2. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH, Hennerici M, for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017-1025.
3. Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, Rosen D, Stewart-Wynne EG, Tuck RR, for the Australian Streptokinase (ASK) Trial Study Group. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA*. 1996;276:961-966.
4. The Multicenter Acute Stroke Trial–Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med*. 1996;335:145-150.
5. The Multicentre Acute Stroke Trial–Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischemic stroke. *Lancet*. 1995;346:1509-1514.
6. Hacke W, Toni D, Steiner T, Kaste M, von Kummer R, Fieschi C, Bluhmki E for the ECASS Study Group. Rt-PA in acute ischemic stroke: results from the ECASS three-hour cohort. *Stroke*. 1997;28:272. Abstract.
7. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, and the TOAST Investigators. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke*. 1993;24:35-41.
8. Shinar D, Gross CR, Bronstein KS, Licata-Gehr EE, Eden DT, Cabrera AR, Fishman IG, Roth AA, Barwick JA, Kunitz SC. Reliability of the activities of daily living scale and its use in the telephone interview. *Arch Phys Med Rehabil*. 1987;68:723-728.
9. Candelise L, Pinardi G, Aritzu E, Musicco M. Telephone interview for stroke outcome assessment. *Cerebrovasc Dis*. 1994;4:341-343.
10. Hosmer DW, Lemeshow S. Model-building strategies and methods for logistic regression. In: Hosmer DW, Lemeshow S, eds. *Applied Logistic Regression*. New York, NY: John Wiley & Sons; 1989:82-134.
11. Bratina P, Greenberg L, Pasteur W, Grotta JC. Current emergency department management of stroke in Houston, Texas. *Stroke*. 1995;26:409-414.
12. The National Institute of Neurological Disorders and Stroke. A National Symposium on Rapid Identification and Treatment of Acute Stroke, December 12-13, 1996, Arlington, Va.
13. Fagan SC, Morgenstern LB, Petitta A, Ward RE, Tilley BC, Marler JR, Broderick JP, Levine SR, Kwiatkowski T, Frankel M, Walker MD, and the NINDS rt-PA Stroke Study Group. rt-PA reduces length of stay and improves disposition following stroke. *Stroke*. 1997;28:272. Abstract.
14. The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA stroke trial. *Stroke*. 1997;28:2119-2125.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997;28:2109-2118.